

SUPPLEMENTARY MATERIALS

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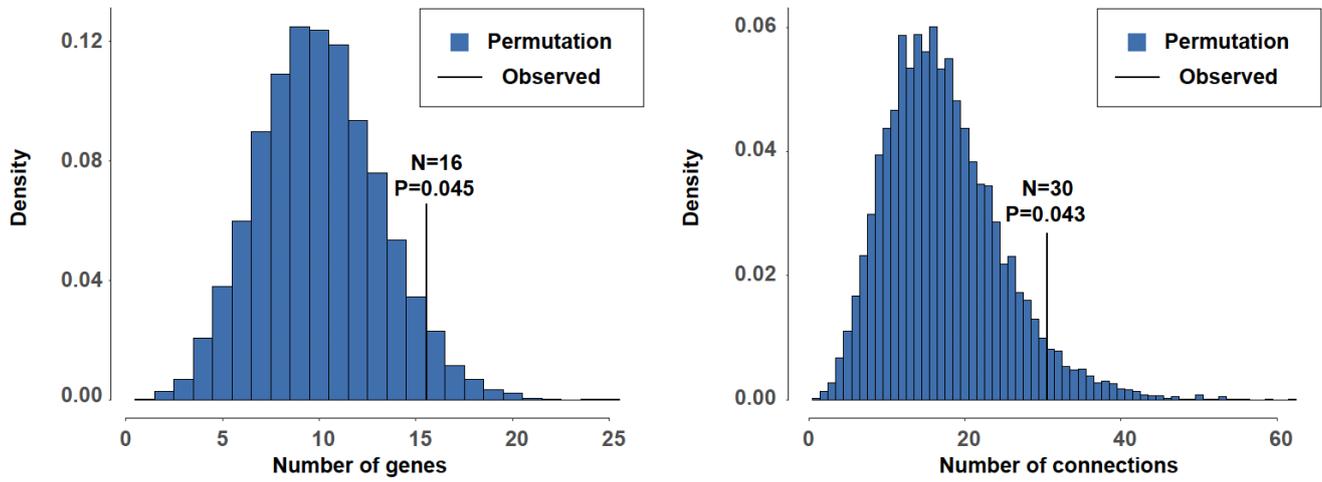
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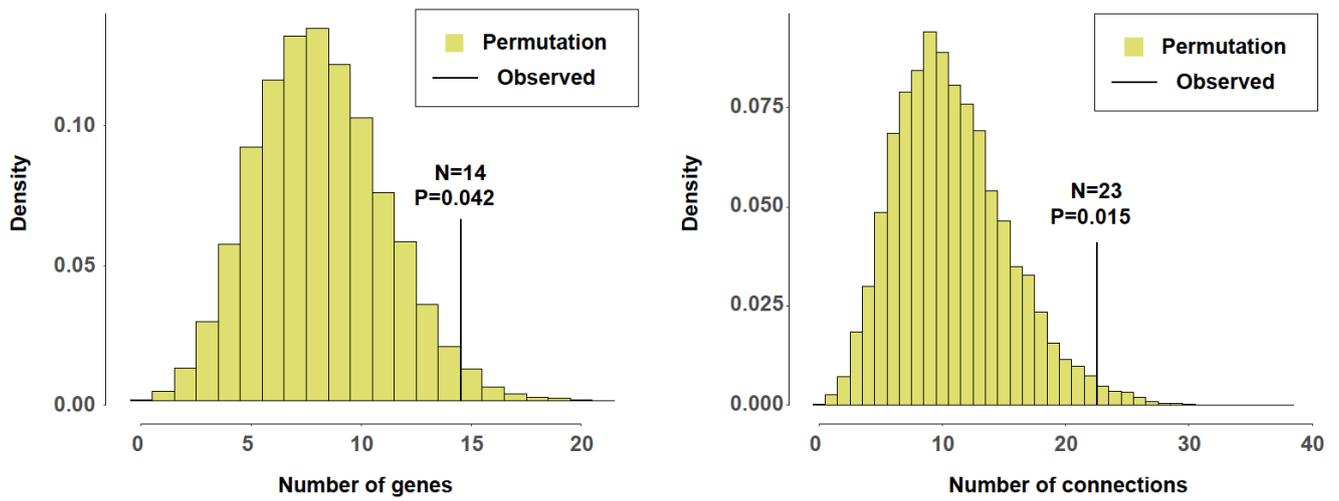


Figure S1. Permutation test of connections between RIGs and DNGs.

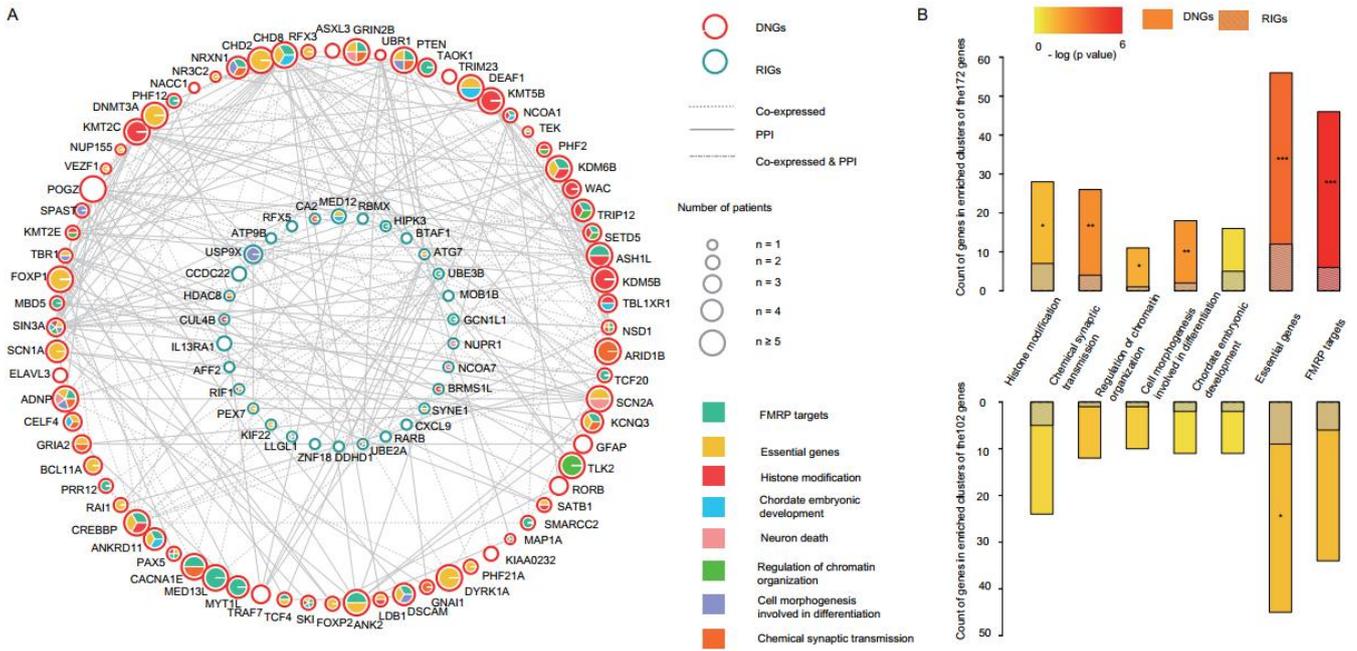


Figure S2. The functional network of 70 RIGs in this study and 102 DNGs from Satterstrom et al.

Table S1. Summary of genes excluded when prioritizing candidate genes.

Gene	Proband	Type	Location (hg19)	Ref	Alt	GenBank No.	Functional effect	Nucleotide change	AA. alteration	MAF in gnomAD	No. of males in gnomAD (<i>n</i>)	pLI	Exclusion reasons
<i>DYNLT3</i>	13311.p1	Hem	chrX:37700357	C	G	NM_006520	SP/Syn	c.198G>C	SP/p.V66V	0.0008	60	0.72	II
<i>FMRI</i>	12390.p1	Hem	chrX:147019617	G	A	NM_002024	SP	c.1126-1G>A	SP	0.001	94	0.65	II
<i>HECW2</i>	11564.p1	Homo	chr2:197208381	G	A	NM_001348768	SP/Mis	c.400C>T	SP/p.P134S	0.0013	-	1	I
<i>LAGE3</i>	14152.p1	Hem	chrX:153706622	A	G	NM_006014	SP/Mis	c.317T>C	SP/p.V106A	1.65E-05	0	0.13	IV
<i>LRCH2</i>	12528.p1	Hem	chrX:114399968	C	T	NM_020871	SP/Mis	c.1355G>A	SP/p.R452K	0.0004	14	1	II
<i>MAP3K15</i>	14181.p1	Hem	chrX:19389462	C	A	NM_001001671	SP	c.3294+1G>T	SP	0.00002	1	0	III
<i>NXT2</i>	12851.p1	Hem	chrX:108779205	A	G	NM_018698	SP/Mis	c.94A>G	SP/p.S32G	0.0004	23	0.83	II
<i>PPP1R3F</i>	12014.p1	Hem	chrX:49142296	G	C	NM_033215	SP/Mis	c.1144G>C	SP/p.V382L	7.38E-06	0	0	IV
<i>SH3BP2</i>	14614.p1	Chet	chr4:2824764	G	A	NM_001122681	SP/Mis	c.239G>A	SP/p.R80Q	0.0004	-	0	I
			chr4:2833298	G	A	NM_001122681	SP/Mis	c.1242G>C	SP/p.Q414H	0	-	0	-
<i>VMA21</i>	14018.p1	Hem	chrX:150573389	C	T	NM_001017980	SP/Syn	c.165C>T	SP/p.G55G	0.001	75	0.57	II
<i>ZNF185</i>	12373.p1	Hem	chrX:152101415	A	C	NM_001178106	SP	c.1020-2A>C	SP	0.0001	8	0	IV
<i>ZNF41</i>	12892.p1	Hem	chrX:47315748	C	T	NM_001324152	SG	c.224G>A	p.W75X	8.17E-05	1	0.04	IV

Chet, compound heterozygous; Homo, Homozygous; Hem, hemizygous; Mis, missense; SP, splicing; FS, frameshift; Syn, synonymous; SG, stop-gain. pLI, probability of loss-of-function intolerance. The exclusion strategies used to prioritize candidate genes were as follows: (I) PTVs recorded as benign variants in the ClinVar database; (II) X-linked inherited PTVs that were present in >10 males in the gnomAD database; (III) genes that harboured biallelically inherited PTVs in the unaffected siblings or harboured X-linked inherited PTVs in male siblings; and (IV) genes in the X chromosome that have a probability of loss-of-function intolerance (pLI) < 0.5, as sourced from the gnomAD database.

Table S2. *De novo* variants in genes with X-linked inherited variants based on the Gene4Denovo database.

Gene	Location (hg19)	Ref	Alt	Effects	Amino acid change	PMID	Disease
<i>CUL4B</i>	119669710	CA	-	frameshift	c.2134_2135del, p.L714Kfs*4	28135719	UDD [1]
<i>HDAC8</i>	71684459	C	T	missense	c.587G>A, p.C196Y	28135719	UDD [1]
<i>HDAC8</i>	71715024	C	T	missense	c.259G>A, p.D87N	28135719	UDD [1]
<i>HDAC8</i>	71684408	C	A	splicing	c.637+1G>T	28135719	UDD [1]
<i>HDAC8</i>	71684432	A	T	stopgain	c.614T>A, p.L205X	28135719	UDD [1]
<i>HDAC8</i>	71715077	A	G	missense	c.206T>C, p.L69P	28135719	UDD [1]
<i>HDAC8</i>	71710788	A	G	missense	exon4:c.346T>C:p.F116L	28135719	UDD [1]
<i>HDAC8</i>	71788721	T	A	stopgain	c.178A>T, p.K60X	28135719	UDD [1]
<i>HDAC8</i>	71684483	A	C	missense	c.563T>G, p.M188R	28135719	UDD [1]
<i>MED12</i>	70342357	G	C	splicing	c.1249-1G>C	27479843	ID [2]
<i>MED12</i>	70342356	A	G	splicing	c.1249-2A>G	27479843	ID [2]
<i>MED12</i>	70349949	T	A	missense	c.3932T>A, p.V1311E	28135719	UDD [1]
<i>MED12</i>	70349262	A	G	missense	c.3674A>G, p.K1225R	28135719	UDD [1]
<i>MED12</i>	70346296	T	C	missense	c.2647T>C, p.S883P	28135719	UDD [1]
<i>MED12</i>	70357668	C	A	stopgain	c.5919C>A, p.Y1973X	28135719	UDD [1]
<i>USP9X</i>	41025217	A	T	missense	c.2078A>T, p.D693V	25363768	ASD [3]
<i>USP9X</i>	41047364	T	A	stopgain	c.3804T>A, p.Y1268X	27479843	ID [2]
<i>USP9X</i>	41031089	A	G	splicing	c.3028-2A>G	27479843	ID [2]
<i>USP9X</i>	41047323	C	T	stopgain	c.3763C>T, p.Q1255X	28135719	UDD [1]
<i>USP9X</i>	41000634	C	T	stopgain	c.1111C>T, p.R371X	28135719	UDD [1]
<i>USP9X</i>	41029317	-	TG	frameshift insertion	c.2706_2707insTG, p.E903Wfs*25	28135719	UDD [1]
<i>USP9X</i>	41000679	A	-	frameshift deletion	c.1156delA, p.M386Wfs*12	28135719	UDD [1]
<i>USP9X</i>	41055613	-	GG	splicing	c.4086+1->GG	28135719	UDD [1]
<i>USP9X</i>	41069824	T	G	missense	c.5078T>G, p.L1693W	28135719	UDD [1]
<i>USP9X</i>	41027299	C	T	missense	c.2464C>T, p.R822C	28135719	UDD [1]

ASD, autism spectrum disorder; ID, intellectual disability; UDD, unspecified neurodevelopmental disorder. The protein truncating variants and deleterious missense variants in X-linked genes were sourced from the Gene4Denovo database [4] (with FDR < 0.1) (<http://genemed.tech/gene4denovo/>).

Table S3. All RIGs in ASD included in this study.

Resource	Recessive inherited genes in ASD
ASC: Ryan N. Doan, et al. Nature Genetics 2019 [5] (<i>n</i> = 41)	<i>ABCC10, ATP9B, BRMS1L, BTAF1, CA2, CDHR3, CGN, CHTF18, COL19A1, CPA4, CXCL9, DDHD1, DNAI2, DYDC1, ELOF1, EML5, FCHSD2, FEV, GCNILI, GZF1, HOXC5, IFITM5, ITPRIPL1, KIF22, LSMEM1, MEDAG, MOB1B, NCOA7, NSUN2, NUPRI, PAH, RARB, RFX5, RIF1, ROGD1, SCGB1D1, SLC1A1, SLC22A6, SLC35E3, USH2A, ZNF16</i>
SSC: this study (<i>n</i> = 21)	<i>AFF2, ANO5, APOO, ATAD3A, ATG7, CCDC22, CUL4B, CYBB, GRIPAP1, HDAC8, HIPK3, IL13RA1, INTS4, LLGL1, MED12, RBMX, RFT1, SLC38A5, UBE2A, USP9X, VPS13B</i>
Maria H. Chahrour, et al. PLoS Genetics 2012 [6] (<i>n</i> = 4)	<i>UBE3B, CLTCL1, NCKAP5L, ZNF18</i>
Timothy W. Yu, et al. Neuron 2013 [7] (<i>n</i> = 6)	<i>AMT, PEX7, SYNE1, VPS13B, PAH, POMGNT1</i>

Variants in *VPS13B* in this study and in Yu et al [7] are the same ones annotated by different transcripts.

Table S4. ASD-associated DNGs sourced from the Gene4denovo database.

Gene	DNV rate	PTV	Dmis	PTV+Dmis	P-value	FDR
<i>CHD8</i>	9.79E-05	10	4	14	2.21E-06	1.97E-13
<i>SCN2A</i>	7.84E-05	5	7	12	2.21E-06	9.20E-11
<i>SYNGAP1</i>	6.85E-05	8	1	9	2.21E-06	2.36E-09
<i>PTEN</i>	1.51E-05	3	6	9	2.21E-06	4.29E-09
<i>KDM5B</i>	6.66E-05	5	4	9	2.21E-06	2.30E-08
<i>SLC6A1</i>	3.14E-05	3	5	8	2.21E-06	7.90E-08
<i>ADNP</i>	4.12E-05	6	0	6	2.21E-06	6.62E-07
<i>SHANK3</i>	5.90E-05	6	0	6	2.21E-06	1.98E-06
<i>ARID1B</i>	9.42E-05	6	1	7	2.21E-06	3.07E-06
<i>DYRK1A</i>	3.32E-05	5	0	5	2.21E-06	8.17E-06
<i>CHD2</i>	7.59E-05	5	1	6	2.21E-06	1.50E-05
<i>GRIN2B</i>	7.56E-05	4	2	6	2.21E-06	3.17E-05
<i>ANK2</i>	1.57E-04	5	2	7	2.21E-06	8.72E-05
<i>TBR1</i>	3.65E-05	2	3	5	2.21E-06	0.00014461
<i>NAA15</i>	3.06E-05	4	0	4	2.21E-06	0.0001966
<i>MYO1E</i>	5.07E-05	3	2	5	2.21E-06	0.00024505
<i>POGZ</i>	6.02E-05	3	2	5	4.42E-06	0.00032561
<i>PPP2R5D</i>	2.84E-05	3	1	4	4.42E-06	0.00042944
<i>FOXP1</i>	3.24E-05	3	1	4	4.42E-06	0.00055067
<i>DNMT3A</i>	5.04E-05	1	4	5	8.84E-06	0.0006939
<i>KMT5B</i>	3.69E-05	3	1	4	8.84E-06	0.00082699
<i>TRIP12</i>	7.91E-05	3	2	5	8.84E-06	0.00098853
<i>STXBP1</i>	3.12E-05	1	3	4	2.21E-05	0.00142246
<i>WAC</i>	2.60E-05	3	0	3	2.65E-05	0.00192332
<i>WDFY3</i>	1.43E-04	3	3	6	2.65E-05	0.0023957
<i>BRD7</i>	2.69E-05	3	0	3	2.65E-05	0.00284594
<i>PIK3CA</i>	3.99E-05	0	4	4	4.86E-05	0.00380694
<i>ASB14</i>	1.12E-05	1	2	3	5.30E-05	0.00479692
<i>NR2F1</i>	2.67E-05	2	1	3	5.74E-05	0.00582972
<i>DSCAM</i>	1.07E-04	4	0	4	7.07E-05	0.00695351
<i>KCNQ2</i>	4.82E-05	3	0	3	7.51E-05	0.00805176
<i>TCF4</i>	3.04E-05	2	1	3	7.51E-05	0.00911506
<i>DDX3X</i>	3.08E-05	2	1	3	7.95E-05	0.01013902
<i>PBX1</i>	1.88E-05	1	2	3	8.40E-05	0.0112337
<i>GALNT18</i>	3.36E-05	2	1	3	8.40E-05	0.01232138
<i>PRPF8</i>	1.15E-04	2	3	5	0.00010605	0.01346538
<i>ASH1L</i>	1.14E-04	4	0	4	0.00010605	0.01455904
<i>NRXN1</i>	7.67E-05	2	2	4	0.00013257	0.01574812
<i>AGO3</i>	3.78E-05	2	1	3	0.00013699	0.01690486
<i>PRKAR1B</i>	2.40E-05	1	2	3	0.00014141	0.01803582
<i>GRIK1</i>	3.85E-05	2	1	3	0.00014582	0.01912965
<i>GIGYF1</i>	5.89E-05	3	0	3	0.00015908	0.02029605
<i>PTPN11</i>	2.75E-05	1	2	3	0.00017676	0.02154851
<i>LMTK3</i>	4.41E-05	2	1	3	0.00020769	0.02292987
<i>TANC2</i>	8.44E-05	2	2	4	0.00021211	0.0243278
<i>RFX3</i>	3.05E-05	1	2	3	0.00021211	0.02567046

<i>TLK2</i>	3.20E-05	1	2	3	0.0002342	0.02709475
<i>FXVD5</i>	9.30E-06	2	0	2	0.0002342	0.02847481
<i>SET</i>	9.53E-06	2	0	2	0.00024304	0.02982169
<i>GRIA2</i>	3.64E-05	1	2	3	0.00033584	0.03151162
<i>ATP1B1</i>	1.38E-05	2	0	2	0.00034026	0.03315995
<i>NUDT17</i>	1.40E-05	2	0	2	0.00034468	0.0347648
<i>ACHE</i>	3.75E-05	1	2	3	0.00035351	0.03637876
<i>ILF2</i>	1.57E-05	2	0	2	0.00038445	0.0380407
<i>SCN1A</i>	8.00E-05	1	3	4	0.00039328	0.03968943
<i>STK33</i>	1.69E-05	2	0	2	0.00044631	0.0413575
<i>PAPOLG</i>	2.90E-05	0	3	3	0.00046399	0.04300868
<i>FANCE</i>	1.85E-05	2	0	2	0.0004905	0.04473589
<i>MECOM</i>	4.13E-05	1	2	3	0.00049492	0.04640494
<i>LAMB1</i>	8.29E-05	1	3	4	0.00051701	0.04810137
<i>NFE2L3</i>	2.04E-05	2	0	2	0.00057446	0.04986466
<i>KATNAL2</i>	2.14E-05	2	0	2	0.00061865	0.05168167
<i>TFAP2C</i>	2.31E-05	2	0	2	0.00066726	0.05363418
<i>ATP1A1</i>	4.59E-05	1	2	3	0.00066726	0.05553142
<i>ASXL3</i>	8.26E-05	3	0	3	0.00073796	0.05750929
<i>SLC4A9</i>	3.62E-05	0	3	3	0.00076005	0.05948667
<i>SPAST</i>	2.51E-05	2	0	2	0.00076889	0.06143745
<i>CELF2</i>	2.52E-05	2	0	2	0.00077773	0.06333949
<i>EYA1</i>	2.58E-05	2	0	2	0.00080866	0.06525474
<i>CALU</i>	9.31E-06	1	1	2	0.00080866	0.06713448
<i>EPHB1</i>	4.96E-05	1	2	3	0.00086169	0.06905605
<i>OR10Z1</i>	1.08E-05	1	1	2	0.00092355	0.07101154
<i>GGNBP2</i>	2.76E-05	2	0	2	0.00093239	0.07292401
<i>UNC80</i>	1.09E-05	1	1	2	0.00093239	0.07478835
<i>TCF7L2</i>	2.82E-05	2	0	2	0.00094565	0.07666498
<i>ANKRD27</i>	5.12E-05	1	2	3	0.0009589	0.07852827
<i>ERII</i>	1.19E-05	1	1	2	0.00097216	0.0803642
<i>RPSA</i>	1.21E-05	1	1	2	0.00099867	0.08217569
<i>SLC6A8</i>	3.02E-05	2	0	2	0.0010738	0.08408828
<i>ERGIC2</i>	1.35E-05	1	1	2	0.00109147	0.08596996
<i>RNF146</i>	1.46E-05	1	1	2	0.00116217	0.08793837
<i>CUL3</i>	3.17E-05	2	0	2	0.00116217	0.08987526
<i>CELF4</i>	3.23E-05	2	0	2	0.00118869	0.09183769
<i>QRICH1</i>	3.25E-05	2	0	2	0.00120636	0.09377518
<i>TSPAN4</i>	1.59E-05	1	1	2	0.00122846	0.09571245
<i>TBL1XR1</i>	1.60E-05	1	1	2	0.00123288	0.0976205
<i>USP15</i>	3.31E-05	2	0	2	0.0012373	0.09949008

Genes with FDR < 0.1 were sourced from the Gene4Denovo database [4] we recently developed (<http://genemed.tech/gene4denovo/>).

Table S5. Functional enrichment of ASD-associated RIGs and DNGs.

Category	P-value_85	P-value_157	Gene symbols
GO:0016570 histone modification	6.35E-10	1.07E-09	RIGs: <u>UBE2A</u> , <u>CUL4B</u> , <u>CPA4</u> , <u>RIF1</u> , <u>HDAC8</u> , <u>BRMS1L</u> , <u>DYDC1</u> DNGs: <u>MECOM</u> , <u>EYA1</u> , <u>SET</u> , <u>TRIP12</u> , <u>USP15</u> , <u>KDM5B</u> , <u>BRD7</u> , <u>KMT5B</u> , <u>WAC</u> , <u>ASH1L</u> , <u>TBL1XR1</u>
GO:0051603 proteolysis involved in cellular protein catabolic process	1.41E-06	2.76E-04	RIGs: <u>UBE2A</u> , <u>USP9X</u> , <u>CUL4B</u> , <u>NUPRI</u> , <u>CCDC22</u> , <u>UBE3B</u> DNGs: <u>PTEN</u> , <u>CUL3</u> , <u>TRIP12</u> , <u>USP15</u> , <u>TLK2</u> , <u>WAC</u> , <u>TBL1XR1</u> , <u>RNF146</u>
GO:0070997 neuron death	4.16E-06	2.02E-05	RIGs: <u>ATG7</u> , <u>NUPRI</u> , <u>NCOA7</u> DNGs: <u>EPHBI</u> , <u>GRIN2B</u> , <u>PIK3CA</u> , <u>SCN2A</u> , <u>SET</u> , <u>STXBP1</u> , <u>SYNGAP1</u> , <u>ADNP</u>
GO:0000904 cell morphogenesis involved in differentiation	2.10E-06	1.96E-06	RIGs: <u>LLGL1</u> , <u>USP9X</u> DNGs: <u>DSCAM</u> , <u>EPHBI</u> , <u>LAMB1</u> , <u>PIK3CA</u> , <u>PTEN</u> , <u>PTPN11</u> , <u>SPAST</u> , <u>STXBP1</u> , <u>CUL3</u> , <u>SYNGAP1</u> , <u>NRXN1</u> , <u>TBRI</u> , <u>ADNP</u> , <u>TANC2</u> , <u>ANKRD27</u> , <u>SHANK3</u>
GO:0007268 chemical synaptic transmission	2.03E-04	4.30E-08	RIGs: <u>CA2</u> , <u>SLC1A1</u> , <u>FCHSD2</u> , <u>CDHR3</u> DNGs: <u>ACHE</u> , <u>EPHBI</u> , <u>GRIA2</u> , <u>GRIK1</u> , <u>GRIN2B</u> , <u>KCNQ2</u> , <u>PRKAR1B</u> , <u>PTEN</u> , <u>SLC6A1</u> , <u>STXBP1</u> , <u>SYNGAP1</u> , <u>NRXN1</u> , <u>ADNP</u> , <u>CELFG4</u> , <u>ARID1B</u> , <u>SHANK3</u>
FMRP targets	4.05E-10	2.96E-11	RIGs: <u>GCN1L1</u> , <u>HIPK3</u> , <u>LLGL1</u> , <u>SYNE1</u> , <u>UBE3B</u> , <u>USP9X</u> DNGs: <u>ADNP</u> , <u>ANK2</u> , <u>ASH1L</u> , <u>ATP1A1</u> , <u>ATP1B1</u> , <u>CHD8</u> , <u>DSCAM</u> , <u>GRIN2B</u> , <u>KCNQ2</u> , <u>LMTK3</u> , <u>NR2F1</u> , <u>NRXN1</u> , <u>PRPF8</u> , <u>PTEN</u> , <u>PTPN11</u> , <u>SHANK3</u> , <u>SLC6A1</u> , <u>STXBP1</u> , <u>SYNGAP1</u> , <u>TANC2</u> , <u>TCF4</u> , <u>TRIP12</u> , <u>WDFY3</u>
Essential genes	5.66E-09	2.69E-09	RIGs: <u>ATG7</u> , <u>COL19A1</u> , <u>FEV</u> , <u>DAC8</u> , <u>KIF22</u> , <u>LLGL1</u> , <u>MED12</u> , <u>PEX7</u> , <u>POMGNT1</u> , <u>RIF1</u> , <u>SYNE1</u> , <u>UBE2A</u> DNGs: <u>ACHE</u> , <u>ADNP</u> , <u>ANK2</u> , <u>ATP1A1</u> , <u>CELFG4</u> , <u>CHD2</u> , <u>CHD8</u> , <u>CUL3</u> , <u>DNMT3A</u> , <u>SCAM</u> , <u>DYRK1A</u> , <u>ERI1</u> , <u>EYA1</u> , <u>FOXP1</u> , <u>GRIA2</u> , <u>GRIN2B</u> , <u>ILF2</u> , <u>KCNQ2</u> , <u>LAMB1</u> , <u>MECOM</u> , <u>MYO1E</u> , <u>NR2F1</u> , <u>PBX1</u> , <u>PIK3CA</u> , <u>PPP2R5D</u> , <u>PTEN</u> , <u>PTPN11</u> , <u>RFX3</u> , <u>RPSA</u> , <u>SCN1A</u> , <u>SCN2A</u> , <u>STXBP1</u> , <u>SYNGAP1</u> , <u>TANC2</u> , <u>TBRI</u> , <u>TCF4</u> , <u>TCF7L2</u> , <u>TFAP2C</u>

P-value_85, the P-value for the 85 genes in the functional network; P-value_157, the P-value for all 157 DNGs and RIGs integrated in this study. Genes contained in the functional network in Figure 2 are underlined.

Table S6. Expression patterns of 70 RIGs and 87 DNGs in ASD.

Gene symbol	Types	Spatio-temporal expression patterns	Prenatal neocortical	Inhibitory and excitatory neuronal expression pattern
<i>ABCC10</i>	RIGs	M0	Ma	Not significant
<i>AFF2</i>	RIGs	M1	Ma	Inhibitory neuronal significant
<i>AMT</i>	RIGs	M2	Mb	Not significant
<i>ANO5</i>	RIGs	M2	Mc	Not significant
<i>APOO</i>	RIGs	M0	Mo	Inhibitory neuronal significant
<i>ATAD3A</i>	RIGs	M0	Mo	Not significant
<i>ATG7</i>	RIGs	M0	Mb	Excitatory neuronal significant
<i>ATP9B</i>	RIGs	M2	Mb	Not significant
<i>BRMS1L</i>	RIGs	M2	Mc	Not significant
<i>BTAFL1</i>	RIGs	M1	Mc	Excitatory neuronal significant
<i>CA2</i>	RIGs	M2	Mo	Inhibitory neuronal significant
<i>CCDC22</i>	RIGs	M0	Mb	Excitatory neuronal significant
<i>CDHR3</i>	RIGs	M1	Ma	Excitatory neuronal significant
<i>CGN</i>	RIGs	M2	Mo	Inhibitory neuronal significant
<i>CHTF18</i>	RIGs	M1	Mb	Excitatory neuronal significant
<i>CLTCL1</i>	RIGs	M1	Ma	Not significant
<i>COL19A1</i>	RIGs	M0	Ma	Not significant
<i>CPA4</i>	RIGs	M2	Mo	Excitatory neuronal significant
<i>CUL4B</i>	RIGs	M1	Mc	Inhibitory neuronal significant
<i>CXCL9</i>	RIGs	M0	Mo	Not significant
<i>CYBB</i>	RIGs	M0	Mb	Not significant
<i>DDHD1</i>	RIGs	M2	Mc	Excitatory neuronal significant
<i>DNAI2</i>	RIGs	M0	Mo	Excitatory neuronal significant
<i>DYDC1</i>	RIGs	M0	Ma	Excitatory neuronal significant
<i>ELOF1</i>	RIGs	M0	Mo	Not significant
<i>EML5</i>	RIGs	M1	Mc	Not significant
<i>FCHSD2</i>	RIGs	M1	Ma	Inhibitory neuronal significant
<i>FEV</i>	RIGs	M2	Mo	Excitatory neuronal significant
<i>GCN1L1</i>	RIGs	M1	Mb	Not significant
<i>GRIPAP1</i>	RIGs	M2	Ma	Not significant
<i>GZF1</i>	RIGs	M2	Mc	Inhibitory neuronal significant
<i>HDAC8</i>	RIGs	M0	Mo	Not significant
<i>HIPK3</i>	RIGs	M2	Mo	Not significant
<i>HOXC5</i>	RIGs	M0	Mo	Not significant
<i>IFITM5</i>	RIGs	M0	Ma	Not significant
<i>IL13RA1</i>	RIGs	M0	Mb	Not significant
<i>INTS4</i>	RIGs	M1	Mo	Not significant
<i>ITPRIPL1</i>	RIGs	M1	Mb	Excitatory neuronal significant
<i>KIF22</i>	RIGs	M1	Mb	Inhibitory neuronal significant
<i>LLGL1</i>	RIGs	M0	Mo	Not significant
<i>LSMEM1</i>	RIGs	M0	Mo	Not significant
<i>MED12</i>	RIGs	M1	Mo	Not significant
<i>MEDAG</i>	RIGs	M0	Mo	Excitatory neuronal significant
<i>MOB1B</i>	RIGs	M1	Mc	Not significant
<i>NCKAP5L</i>	RIGs	M1	Ma	Inhibitory neuronal significant

<i>NCOA7</i>	RIGs	M2	Ma	Excitatory neuronal significant
<i>NSUN2</i>	RIGs	M1	Mo	Excitatory neuronal significant
<i>NUPR1</i>	RIGs	M0	Mb	Not significant
<i>PAH</i>	RIGs	M2	Mo	Not significant
<i>PEX7</i>	RIGs	M2	Mc	Not significant
<i>POMGNT1</i>	RIGs	M0	Ma	Not significant
<i>RARB</i>	RIGs	M0	Mo	Not significant
<i>RBMX</i>	RIGs	M1	Mb	Inhibitory neuronal significant
<i>RFT1</i>	RIGs	M0	Mb	Not significant
<i>RFX5</i>	RIGs	M2	Mb	Inhibitory neuronal significant
<i>RIF1</i>	RIGs	M1	Mc	Inhibitory neuronal significant
<i>ROGDI</i>	RIGs	M2	Ma	Excitatory neuronal significant
<i>SCGB1D1</i>	RIGs	M0	Mo	Not significant
<i>SLC1A1</i>	RIGs	M0	Ma	Inhibitory neuronal significant
<i>SLC22A6</i>	RIGs	M0	Mo	Excitatory neuronal significant
<i>SLC35E3</i>	RIGs	M1	Mc	Not significant
<i>SLC38A5</i>	RIGs	M0	Mb	Not significant
<i>SYNE1</i>	RIGs	M2	Ma	Not significant
<i>UBE2A</i>	RIGs	M0	Mc	Not significant
<i>UBE3B</i>	RIGs	M2	Mo	Not significant
<i>USH2A</i>	RIGs	M2	Mo	Excitatory neuronal significant
<i>USP9X</i>	RIGs	M1	Ma	Not significant
<i>VPS13B</i>	RIGs	M1	Mo	Not significant
<i>ZNF16</i>	RIGs	M1	Mo	Not significant
<i>ZNF18</i>	RIGs	M1	Ma	Excitatory neuronal significant
<i>ACHE</i>	DNGs	M2	Ma	Inhibitory neuronal significant
<i>ADNP</i>	DNGs	M1	Mc	Inhibitory neuronal significant
<i>AGO3</i>	DNGs	M1	Mo	Excitatory neuronal significant
<i>ANK2</i>	DNGs	M0	Mo	Excitatory neuronal significant
<i>ANKRD27</i>	DNGs	M1	Ma	Excitatory neuronal significant
<i>ARID1B</i>	DNGs	M1	Mo	Not significant
<i>ASB14</i>	DNGs	M1	Mo	Not significant
<i>ASH1L</i>	DNGs	M2	Mo	Not significant
<i>ASXL3</i>	DNGs	M1	Ma	Excitatory neuronal significant
<i>ATP1A1</i>	DNGs	M2	Ma	Inhibitory neuronal significant
<i>ATP1B1</i>	DNGs	M2	Mo	Inhibitory neuronal significant
<i>BRD7</i>	DNGs	M1	Mb	Not significant
<i>CALU</i>	DNGs	M1	Mb	Not significant
<i>CELF2</i>	DNGs	M1	Mc	Excitatory neuronal significant
<i>CELF4</i>	DNGs	M2	Ma	Excitatory neuronal significant
<i>CHD2</i>	DNGs	M1	Mo	Not significant
<i>CHD8</i>	DNGs	M1	Ma	Not significant
<i>CUL3</i>	DNGs	M1	Ma	Not significant
<i>DDX3X</i>	DNGs	M1	Mo	Not significant
<i>DNMT3A</i>	DNGs	M1	Mo	Excitatory neuronal significant
<i>DSCAM</i>	DNGs	M1	Ma	Excitatory neuronal significant
<i>DYRK1A</i>	DNGs	M1	Mc	Excitatory neuronal significant
<i>EPHB1</i>	DNGs	M1	Ma	Not significant
<i>ERGIC2</i>	DNGs	M0	Mc	Inhibitory neuronal significant

<i>ERII</i>	DNGs	M1	Mc	Excitatory neuronal significant
<i>EYA1</i>	DNGs	M0	Mo	Not significant
<i>FANCE</i>	DNGs	M1	Ma	Inhibitory neuronal significant
<i>FOXP1</i>	DNGs	M0	Ma	Excitatory neuronal significant
<i>FXYD5</i>	DNGs	M0	Mb	Excitatory neuronal significant
<i>GALNT18</i>	DNGs	M2	Ma	Not significant
<i>GGNBP2</i>	DNGs	M1	Ma	Excitatory neuronal significant
<i>GIGYF1</i>	DNGs	M0	Mo	Not significant
<i>GRIA2</i>	DNGs	M2	Ma	Excitatory neuronal significant
<i>GRIK1</i>	DNGs	M2	Mo	Inhibitory neuronal significant
<i>GRIN2B</i>	DNGs	M0	Ma	Inhibitory neuronal significant
<i>ILF2</i>	DNGs	M1	Mo	Not significant
<i>KATNAL2</i>	DNGs	M2	Mo	Not significant
<i>KCNQ2</i>	DNGs	M1	Mb	Excitatory neuronal significant
<i>KDM5B</i>	DNGs	M1	Mo	Excitatory neuronal significant
<i>KMT5B</i>	DNGs	M1	Ma	Not significant
<i>LAMB1</i>	DNGs	M0	Ma	Excitatory neuronal significant
<i>LMTK3</i>	DNGs	M0	Ma	Inhibitory neuronal significant
<i>MECOM</i>	DNGs	M0	Mo	Not significant
<i>MYO1E</i>	DNGs	M0	Mb	Excitatory neuronal significant
<i>NAA15</i>	DNGs	M1	Mc	Not significant
<i>NFE2L3</i>	DNGs	M1	Ma	Not significant
<i>NR2F1</i>	DNGs	M1	Mo	Not significant
<i>NRXN1</i>	DNGs	M0	Ma	Not significant
<i>NUDT17</i>	DNGs	M0	Mo	Not significant
<i>OR10Z1</i>	DNGs	M0	Mo	Not significant
<i>PAPOLG</i>	DNGs	M1	Mc	Not significant
<i>PBX1</i>	DNGs	M1	Ma	Not significant
<i>PIK3CA</i>	DNGs	M1	Mc	Not significant
<i>POGZ</i>	DNGs	M1	Ma	Excitatory neuronal significant
<i>PPP2R5D</i>	DNGs	M0	Ma	Not significant
<i>PRKAR1B</i>	DNGs	M2	Mo	Excitatory neuronal significant
<i>PRPF8</i>	DNGs	M1	Mo	Inhibitory neuronal significant
<i>PTEN</i>	DNGs	M1	Mc	Excitatory neuronal significant
<i>PTPN11</i>	DNGs	M2	Mo	Excitatory neuronal significant
<i>QRICH1</i>	DNGs	M1	Ma	Not significant
<i>RFX3</i>	DNGs	M1	Mc	Not significant
<i>RNF146</i>	DNGs	M1	Mc	Excitatory neuronal significant
<i>RPSA</i>	DNGs	M1	Ma	Not significant
<i>SCN1A</i>	DNGs	M2	Ma	Inhibitory neuronal significant
<i>SCN2A</i>	DNGs	M2	Ma	Excitatory neuronal significant
<i>SET</i>	DNGs	M1	Mo	Not significant
<i>SHANK3</i>	DNGs	M2	Ma	Not significant
<i>SLC4A9</i>	DNGs	M2	Ma	Not significant
<i>SLC6A1</i>	DNGs	M2	Mb	Inhibitory neuronal significant
<i>SLC6A8</i>	DNGs	M2	Mb	Not significant
<i>SPAST</i>	DNGs	M1	Mc	Not significant
<i>STK33</i>	DNGs	M0	Mb	Excitatory neuronal significant
<i>STXBP1</i>	DNGs	M2	Ma	Excitatory neuronal significant

<i>SYNGAP1</i>	DNGs	M0	Mo	Excitatory neuronal significant
<i>TANC2</i>	DNGs	M1	Ma	Excitatory neuronal significant
<i>TBLXR1</i>	DNGs	M1	Mc	Excitatory neuronal significant
<i>TBR1</i>	DNGs	M1	Ma	Excitatory neuronal significant
<i>TCF4</i>	DNGs	M1	Mo	Inhibitory neuronal significant
<i>TCF7L2</i>	DNGs	M0	Mb	Excitatory neuronal significant
<i>TFAP2C</i>	DNGs	M1	Mb	Not significant
<i>TLK2</i>	DNGs	M1	Mo	Not significant
<i>TRIP12</i>	DNGs	M1	Mc	Excitatory neuronal significant
<i>TSPAN4</i>	DNGs	M0	Ma	Inhibitory neuronal significant
<i>UNC80</i>	DNGs	M2	Ma	Excitatory neuronal significant
<i>USP15</i>	DNGs	M1	Ma	Excitatory neuronal significant
<i>WAC</i>	DNGs	M2	Mc	Excitatory neuronal significant
<i>WDFY3</i>	DNGs	M0	Mc	Not significant

Genes contained in M0 and Mo were not clustered into any co-expression modules by weighted correlation network analysis.

Table S7. Comparison of expression patterns between DNGs and RIGs in ASD, ID and CHD.

Disorder	Gene (<i>n</i>)	Spatio-temporal				Prenatal neocortical			Exc and Inh neurons		
		M1	M2	M0	Ma	Mb	Mc	Mo	Exc	Inh	Not sig
ASD-Wang	DNGs (87)	47	20	20	35	10	16	26	35	14	38
	RIGs (70)	23	20	27	17	15	12	26	18	13	39
	P-value	2.21E-02	0.46	-	4.13E-02	0.12	1	-	0.063	0.83	-
	OR	2.19	0.75	-	2.09	0.48	1.09	-	1.94	0.84	-
	95% CI	1.08-4.49	0.34-1.64	-	1.00-4.50	0.18-1.24	0.44-2.74	-	0.93-4.12	0.34-2.12	-
ASD-Satterstrom	DNGs (102)	66	18	18	61	9	13	28	39	22	41
	RIGs (70)	25	19	26	23	14	12	35	18	13	39
	P-value	2.02E-04	0.19	-	6.25E-04	0.041	0.51	-	0.10	0.7	-
	OR	3.28	0.58	-	3.02	0.39	0.71	-	1.78	1.2	-
	95% CI	1.67-6.56	0.26-1.28	-	1.54-6.06	0.14-1.39	0.28-1.83	-	0.88-3.72	0.53-2.83	-
ID	DNGs (82)	45	18	19	31	13	13	25	25	15	42
	RIGs (120)	51	26	43	41	15	13	51	21	29	70
	P-value	0.088	1	-	0.65	0.54	0.39	-	0.040	0.39	-
	OR	1.64	1.02	-	1.17	1.32	1.55	-	2.06	0.7	-
	95% CI	0.90-3.01	0.48-2.11	-	0.62-2.19	0.54-3.18	0.62-3.86	-	1.01-4.26	0.32-1.48	-
CHD	DNGs (78)	42	14	22	21	18	12	27	28	12	38
	RIGs (88)	43	17	28	23	24	15	26	32	12	44
	P-value	0.53	0.84	-	1	0.59	0.84	-	1	0.83	-
	OR	1.22	0.91	-	1.04	0.8	0.89	-	0.98	1.15	-
	95% CI	0.63-2.35	0.38-2.15	-	0.49-2.20	0.37-1.71	0.35-2.19	-	0.49-1.94	0.44-3.01	-

ASD, autism spectrum disorder; ID, intellectual disability; CHD, congenital heart defects; Exc, excitatory neurons; Inh, inhibitory neurons; OR, odds ratio; CI, confidence interval; RIGs, recessive inherited genes; DNGs, genes with *de novo* variants. In the panels of ASD-Wang and ASD-Satterstrom, the RIGs were sourced from Table S3 and the DNGs were sourced from the Gene4Denovo database [4] and Satterstrom et al [8], respectively. In the ID panel, the RIGs were sourced from the OMIM database, and the DNGs were sourced from the Gene4Denovo database [4]. In the CHD panel, the RIGs were sourced from Jin et al [9] and the DNGs were sourced from Gene4Denovo database [4]. Genes in M0 and Mo were not clustered into any co-expression modules by weighted correlation network analysis. We used Fisher's exact test to perform enrichment analysis. P-values <0.05 are highlighted in bold.

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